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Direct Deprotonative Functionalization of α,α -Difluoromethyl Ketones using a Catalytic Organosuperbase

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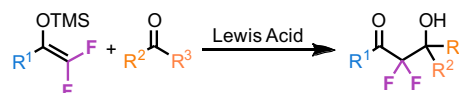
Abstract: The deprotonative functionalization of α,α -difluoromethyl ketones is described herein. Using a catalytic organosuperbase and a silane additive, the corresponding difluoroenolate could be generated and trapped with aldehydes to deliver various α,α -difluoro- β -hydroxy ketones in high yields. This new strategy tolerates numerous functional groups and represents the access to the difluoroenolate by direct deprotonation of the difluoromethyl unit. The diastereoselective version of the reaction was also investigated with *d.r.* up to 93:7. Several transformations were performed to demonstrate the synthetic potential of these α,α -difluoro- β -hydroxy ketones. In addition, this method has been extended to the use of other electrophiles such as imines and chalcogen derivatives, and a difluoromethyl sulfoxide as nucleophile, thus leading to a diversity of difluoromethylene compounds.

Introduction

Fluorinated molecules often lead to unique bioactivities compared to their non-fluorinated analogs.^[1] Currently, 53% of agrochemicals^[2] and 18% of pharmaceuticals^[3] entering the global market contain at least one fluorine atom. Among fluorine synthons, the difluoromethylene group is an attractive structural motif^[4] and presents a great importance in medicinal chemistry thanks to its bioisosteric relationship with the carbonyl motif and the oxygen atom.^[1c] In particular, α,α -difluoromethyl ketones and α,α -difluoro- β -hydroxy ketones are versatile building-blocks allowing access to various difluoromethylene compounds.^[5] Furthermore, bioactive molecules containing the difluoroketone unit have proved to be efficient inhibitors of many enzymes such as the HIV protease or the GABA_B receptor due to their ability to form stable hydrates, hemiacetals or acetals.^{[5b],[6]} The generation of difluoroenolate is a method of choice to construct difluoroketone substructures.^[7] Several strategies have already been developed for the preparation of α,α -difluoro- β -hydroxy ketones involving diverse precursors leading to the enolate (Scheme 1).^[8-15] Many of these routes involve Mukaiyama aldol reactions *via* synthesis of the difluoroenol silyl ether^[8] or Reformatsky-type reactions.^[9] However, these approaches suffer drawbacks like the poor stability of the silyl enol ether or the use of stoichiometric amounts of organometallic reagents. Other strategies allowing for milder conditions have been described.

Selected examples of previous aldol-type reactions in the literature

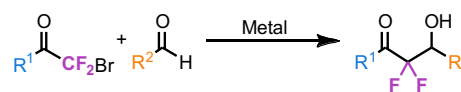
Mukaiyama-aldol reaction by Zhou *et al.*



• Poor stability of silyl enol ether

42 examples
42-98%

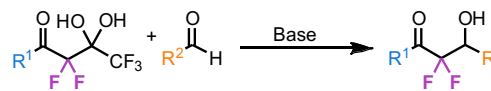
Reformatsky reaction by Liu *et al.*



• Stoichiometric metal use

16 examples
40-86%

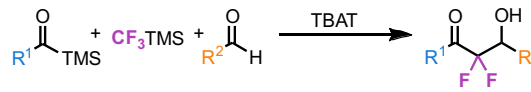
Trifluoroacetate release by Colby *et al.*



• Pre-functionalization of the substrate

16 examples
64-95%

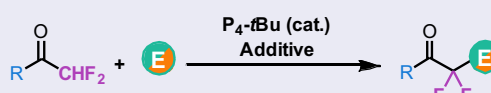
Brook rearrangement/fluoride elimination by Leclerc *et al.*



• Indirect method
• Difficult access to acyl silanes

18 examples
38-70%

This work: Deprotonative functionalization of difluoromethyl ketones



• Direct deprotonative functionalization
• No pre-functionalization
• Metal-free
• Various electrophiles

36 examples
30-95%

Scheme 1. Selected examples to access α,α -difluoro- β -hydroxy ketones and our strategy.

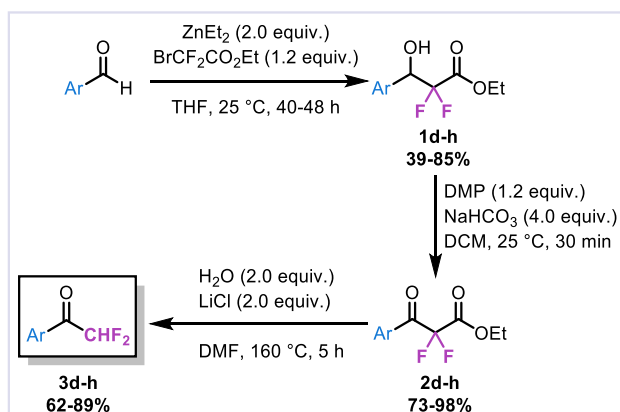
such as the trifluoroacetate release to generate the difluoroenolate from a stable precursor developed by Colby *et al.*^[10c] However, this method requires the pre-functionalization of the substrate. A Brook rearrangement/fluoride elimination process was also disclosed by Leclerc *et al.*^[11a] but this strategy

is limited by the difficult access to the acyl silanes. More significantly, none of these methods report the direct deprotonation of α,α -difluoromethyl ketones presumably because of the poor stability of the generated carbanion leading to the corresponding fluorocarbene due to electronic repulsion.

In this context, our group focused on the deprotonation of difluoromethyl scaffolds^[16] and we already reported the deprotonation of difluoromethyl sulfoxides to access α,α -difluoro- β -hydroxy sulfoxides using the Schwesinger superbase (P_4 -*t*Bu).^[16c-d] This base was already demonstrated by Shibata and Mikami^[17] to stabilize “naked” α -fluorinated carbanions by the counterion P_4 -*t*Bu/ H^+ with increased reactivity towards electrophiles. Its catalytic use has been highlighted by both Mikami's^[17d] and Shibata's^[17b] groups when employing silylated additives such as 1-trimethylsilylpropyne (TMSP) or tris(trimethylsilyl)amine, respectively. These additives could act as a relay base or regenerate the P_4 -*t*Bu base.^[17b, 18] Herein, inspired by this new “superbase organocatalyst system”, we desired to develop the unprecedented deprotonative functionalization of α,α -difluoromethyl ketones using sub-stoichiometric amounts of the P_4 -*t*Bu base in the presence of aldehydes as first electrophiles to access highly valuable difluoromethylene compounds.

Results and Discussion

Firstly, α,α -difluoromethyl ketones **3a-c**,^[19] **3e**^[20], **3i-j**^[19], **3k**,^[21] **3l**^[22] and **3m**^[23] were prepared following reported procedures in the literature (see Supporting Information for details). To synthesize unknown α,α -difluoromethyl ketones **3d-h**, we designed a new strategy relying on cheap aldehydes as starting materials (Scheme 2). A Reformatsky-type reaction was performed to afford the corresponding hydroxy esters **1** that were further oxidized with DMP. The last step involved a Krapcho dealkoxycarbonylation to obtain the desired ketone **3**. This three-step methodology is efficient, practical and only implies the use of non-expensive reagents (see Supporting Information for more details).



Scheme 2. Synthesis of aryl α,α -difluoromethyl ketones (see Supporting Information for more details).

Then we started to investigate the aldol reaction using mesityl ketone **3g** and *p*-anisaldehyde (Table 1). These compounds are substrates of choice since the corresponding signals in NMR

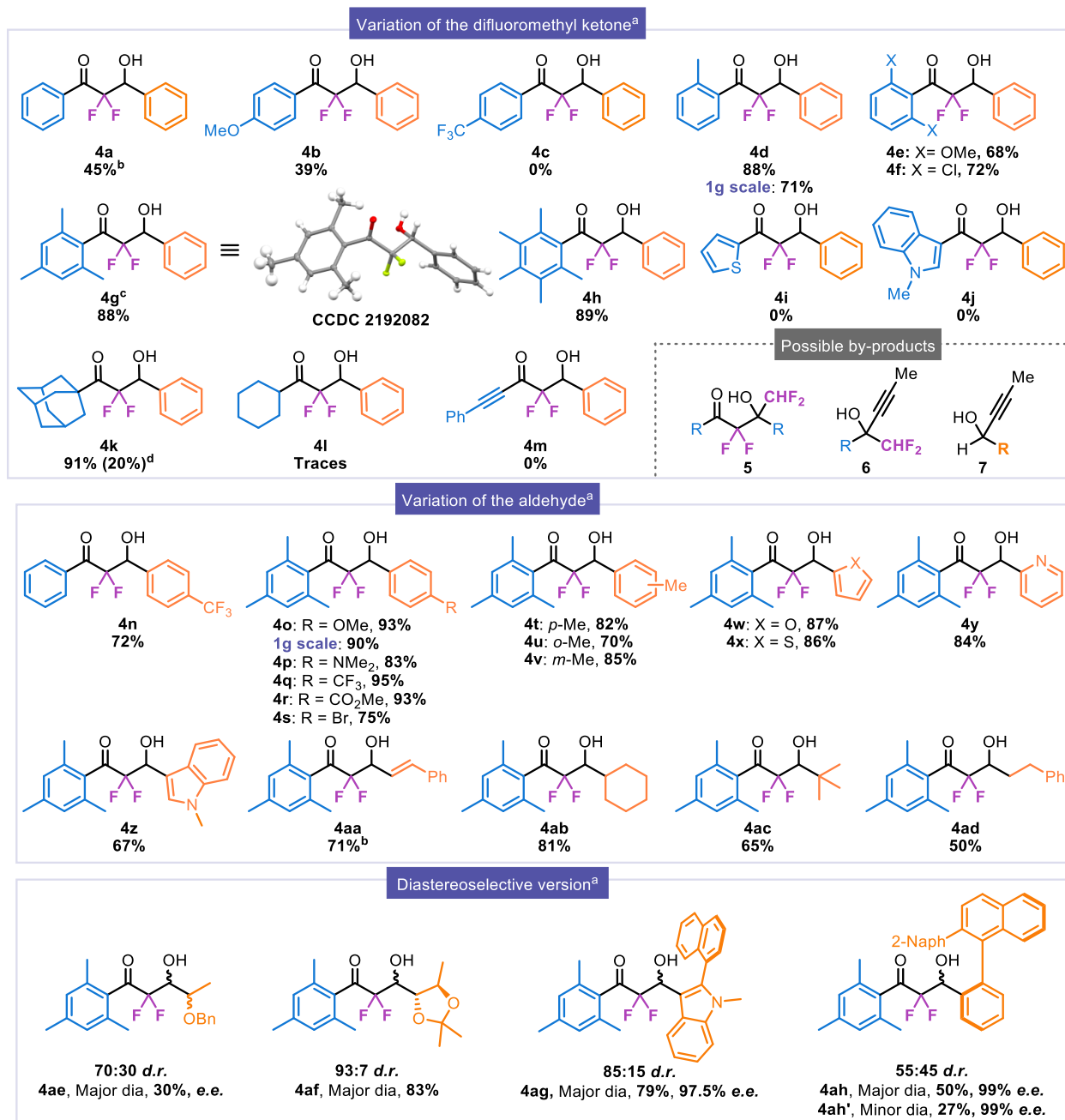
facilitate the reaction monitoring. Furthermore, since the mesityl ketone **3g** is not volatile unlike many difluoromethyl ketones, its use is more convenient. Inspired by Mikami's^[17d] and Shibata's^[17b] reports and after a slight optimization, our best conditions were defined as follows: 1.0 equivalents of α,α -difluoromethyl ketone, 1.2 equivalents of aldehyde, 1.5 equivalents of TMSP, 10 mol% of P_4 -*t*Bu in THF ($C = 0.66M$) at 25 °C for 24 h under argon atmosphere. Delightfully, under these conditions and after desilylation with TBAF, the targeted product **4i** was obtained in a high isolated yield of 93% (Entry 1). By employing tris(trimethylsilyl)amine ($N(TMS)_3$), a similar yield of 90% was achieved (Entry 2). A control experiment showed that no reaction occurs in the absence of the P_4 -*t*Bu base (Entry 3). Another additional experiment was conducted without TMSP leading to a significantly lower yield of 43% (Entry 4). The use of another base such as KHMDS did not lead to an effective transformation with only 32% yield (Entry 5). In this case, the K^+ counterion is presumably more coordinating thus making the formed anion less reactive, whereas P_4 -*t*Bu/ H^+ allows the formation of a “naked” carbanion with increased nucleophilicity.^[16] In addition, unmasking the alkyne by fluoride-promoted desilylation with CsF or AgF was ineffective (Entry 6 and 7). Finally, DMF was used as an alternative solvent, since it is known to stabilize fluorinated carbanions by forming hemiaminolate species^[24] but the yield drastically decreased to 59% (Entry 8).

Table 1. Optimized conditions and deviation effect.^[a]

Entry	Deviation from standard conditions	Yield (%) ^[b]
1	None	93
2	$N(TMS)_3$ instead of TMSP	90
3	Without P_4 - <i>t</i> Bu	0
4	Without TMSP	43
5	KHMDS instead of P_4 - <i>t</i> Bu	32
6	CsF instead of P_4 - <i>t</i> Bu	Traces
7	AgF instead of P_4 - <i>t</i> Bu	Traces
8	DMF instead of THF	59

[a] See the Supporting Information for more details. [b] Isolated yield.

Next, with the optimal conditions in hand, we decided to investigate the scope and limitations of this organocatalytic aldol reaction using various difluoromethyl ketones with benzaldehyde as the electrophile (Scheme 3). When employing difluoroaceto-



[a] Reaction conditions: ketone (1.0 equiv.), aldehyde (1.2 equiv.), 1-trimethylsilylpropyne (1.5 equiv.), P_4-tBu (10 mol%), THF ($C = 0.66M$), 25 °C, until completion (16-24h); [b] ^{19}F NMR yield, determined using fluorobenzene as internal standard; [c] ORTEP structure of **4g** (CCDC 2192082);^[25] ellipsoids at the 30% probability level; [d] 91% obtained with $N(TMS)_3$ and 20% obtained with 1-trimethylsilylpropyne.

Scheme 3. Scope of the deprotonative functionalization of α,α -difluoromethyl ketones in the presence of aldehydes to access α,α -difluoro- β -hydroxy ketones.

phenone **3a**, the desired compound **4a** was observed in 45% ^{19}F NMR yield along with the by-product **5** coming from the self-condensation of **3a**. In addition, we never managed to obtain compound **4a** as a pure sample due to degradation during purification as also described by Leclerc *et al.* for the same product.^[11a] In order to avoid the formation of the by-product, a methoxy group was introduced in the *para* position leading to aldol **4b** in 39% yield. On the contrary, with a α - CF_3 substituent, the desired product **4c** was not obtained and only the self-condensation adduct was identified. The use of *ortho* di-

substituted ketones with methoxy or chloro moieties led to similar yields of 68% and 72% (**4e-f**), respectively. As well, we performed the reaction with mesityl and pentamethyl difluoromethyl ketones to access the aldols **4g-h** in high yields. The structure of derivative **4g** was confirmed by X-ray crystallography.^[25] Furthermore, heteroaryl ketones were employed such as thiophene or indole derivatives without any success as only traces of the desired aldols were observed. Finally, the reaction was carried out with aliphatic ketones. When adamantyl ketone was reacted under the optimized conditions, product **4k** was only obtained in 20% yield

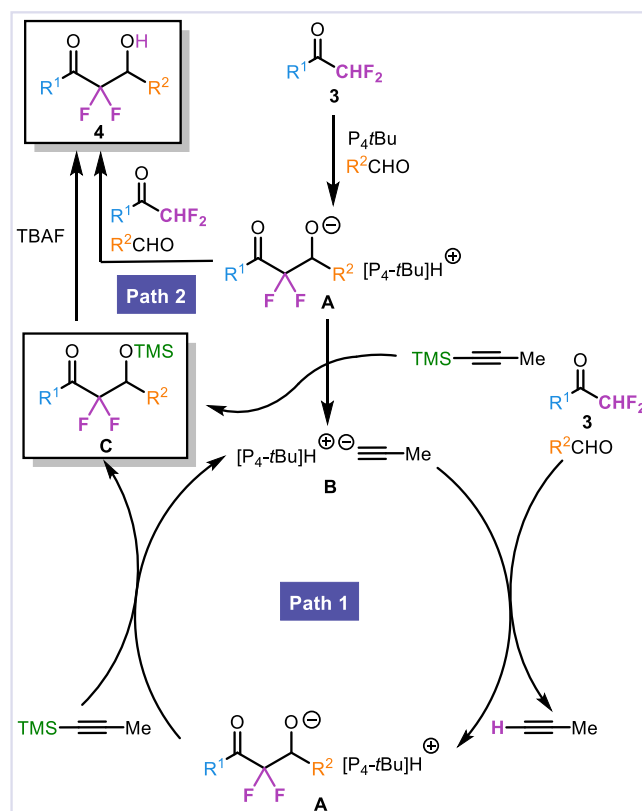
along with two side products **6** and **7** coming from the addition of the alkynide to the ketone and aldehyde starting materials (see mechanism below). By switching the silane source to $N(\text{TMS})_3$ to overcome the generation of **6** and **7**, an excellent yield of 91% was obtained, probably due to the lower nucleophilicity of the silane employed. Then, by conducting the reaction with an enolizable ketone such as a cyclohexyl derivative, only traces of the aldol **4i** were detected and the substrate was fully recovered. An ynone was also used but without success since a complete degradation of the latter was observed.

In summary, the substituents linked to the aryl difluoromethyl ketone have a significant role since the reaction is more efficient with electron-rich and *ortho*-substituted aryl ketones. On the one hand, the introduction of electron-donating substituents allows to limit/avoid the formation of the self-condensation side product by decreasing the electrophilicity of the ketone. On the other hand, regarding *ortho*-substituted substrates, the bulky aromatic ring is twisted out of conjugation, thus protecting the carbonyl from this dimerization. Concerning aliphatic ketones, only the non-enolizable derivatives seem to be tolerated, probably due to a deprotonation competition on both sides of the carbonyl function.^[9c]

To follow our investigations, we then evaluated the impact of the starting aldehyde on the course of the reaction. Interestingly, difluoroacetophenone **3a** and *para*-trifluoromethyl benzaldehyde afforded the corresponding aldol **4n** in 70% yield. As anticipated, the use of a more electron-poor electrophile instead of benzaldehyde prevents the dimerization of the ketone. Then, diverse aldehydes were reacted with the mesityl ketone **3g**. Aryl aldehydes bearing electron-donating or electron-withdrawing groups at the *para* position of the phenyl ring gave the targeted products **4o-t** in good yields (68-88%). *Ortho*- and *meta*-substituted benzaldehydes also gave excellent results with yields up to 85% (**4u-v**). Pleasingly, heteroaryl aldehydes such as furan, pyridine or indole derivatives provided products **4w-z** in satisfying yields (67-87%). The reaction was also performed with cinnamaldehyde leading to the 1,2-addition product **4aa** in 71% ¹⁹F NMR yield. The use of alkyl aldehydes (enolizable or not) allowed the access to the desired compounds **4ab**, **4ac**, **4ad** in moderate to good yields ranging from 50 to 81%. We also demonstrated the feasibility of this aldol reaction on a gram scale (1 gram of **3d** gave 71% of **4d** and 1 gram of **3g** gave 90% of **4g**). Afterwards, we developed the diastereoselective version of this aldol reaction using enantiopure and/or diastereopure aldehydes. Gratifyingly, with 2-(benzyloxy)propionaldehyde displaying central chirality, a good *d.r.* (70:30) was achieved and the major diastereoisomer **4ae** was isolated in 30% yield. Unfortunately, this diastereoisomer was obtained as a racemic mixture probably due to a racemization of the parent aldehyde during the reaction (with reprotonation by the aldehyde or the difluoroketone). Conversely, a related aldehyde with two contiguous stereocenters involved in an acetonide moiety led to **4af** in 83% yield, 93:7 *d.r.* and >99% *e.e.* We then employed an atropisomeric (hetero)biaryl described by Wencel-Delord and Ackermann,^[26] and the targeted product **4ag** was obtained in a high yield with 85:15 *d.r.* and 97.5% *e.e.* The atropisomeric biaryl reported by Shi *et al.*^[27] gave the corresponding aldols **4ah-ah'** in a low *d.r.* of 55:45. However, the diastereoisomers were separated by column chromatography and obtained with 99% *e.e.*

Based on previous reports by Mikami^[17d] and Shibata,^[17b] a plausible mechanism can be proposed for this aldol-type reaction

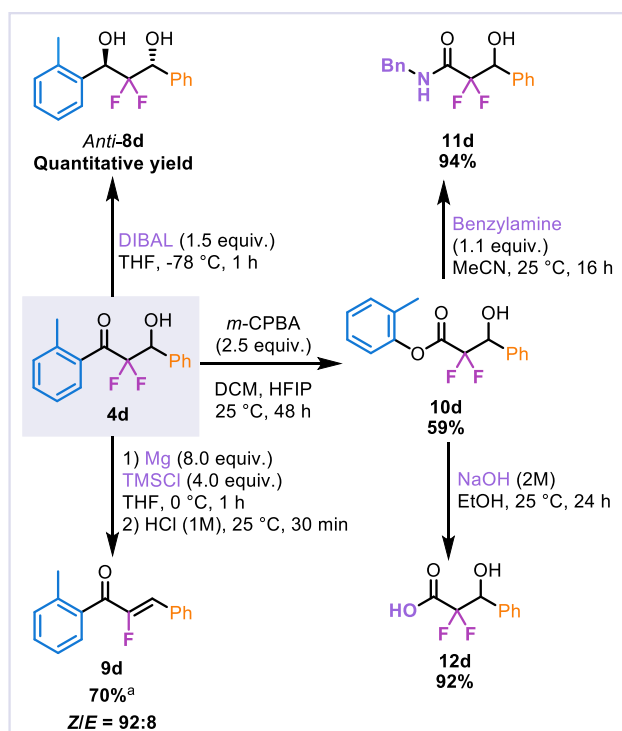
(Scheme 4). According to our observations, the mechanism would imply two pathways. The path one would firstly involve the deprotonation of the difluoromethyl ketone **3** by the $P_4-t\text{Bu}$ base and condensation on the aldehyde to form the ion pair **A**. The generated alkoxide should activate the trimethylsilyl group on the alkyne to access the desired compound **C**. At this time, the formed alkynide **B** would act as a base to deprotonate another equivalent of the ketone. The generated carbanion could then react with the aldehyde forming again the ion pair **A**, leading to the targeted product **C** after reaction with TMSP. Prior to desilylation, the silyl ether **C** was observed by analysis of the crude mixture, thus supporting our mechanistic hypothesis. As the reaction can still proceed without the silane, although a significantly lower yield was obtained (*i.e.* 43% vs 93% with TMSP), a complementary mechanism was considered. This second pathway relies on the deprotonation of the ketone **3** by the alkoxide formed leading directly to the aldol **4**. However, in the presence of TMSP, the generation of volatile propyne seems to be a putative driving force in this aldol process. Notably in both pathways and as described by Mikami^[17d] and Shibata,^[17b] the counterion $P_4-t\text{Bu}/\text{H}^+$ is supposed to play an important role in this mechanism. The latter might indeed form a stabilized ion pair with the alkoxide and by its non-coordinating character, enhance the nucleophilicity of the anion.



Scheme 4. Proposed mechanism to access α,α -difluoro- β -hydroxy ketones.

In addition, following our hypothesis and in accordance with the literature, the $P_4-t\text{Bu}$ base should not be regenerated during the reaction given its high basicity ($\text{p}K_a = 42.6$ in MeCN).^[28] To shed light on the mechanism, we monitored the aldol reaction by ³¹P NMR for several hours (see Supporting Information for more details) and only the protonated base was detected, thus supporting our assumption.

Finally, to exploit the synthetic potential of our α,α -difluoro- β -hydroxy ketones, we carried out several transformations (Scheme 5). First, a diastereoselective reduction using DIBAL allowed us to form the *anti*-diol **8d** in a quantitative yield. Then, in the presence of magnesium and trimethylsilyl chloride, the α -monofluorinated ketone **9d** was isolated in 70% ^{19}F NMR yield with a satisfying *Z/E* ratio of 92:8. Unfortunately, no pure sample was obtained due to degradation during purification by flash chromatography on silica gel. Next, to convert the aryl moiety introduced by the difluoroketone into a more transformable group, a Baeyer-Villiger oxidation provided the corresponding β -hydroxy ester **10d** in an unoptimized 59% yield. This product was then converted into amide **11d** and carboxylic acid **12d** with excellent yields.

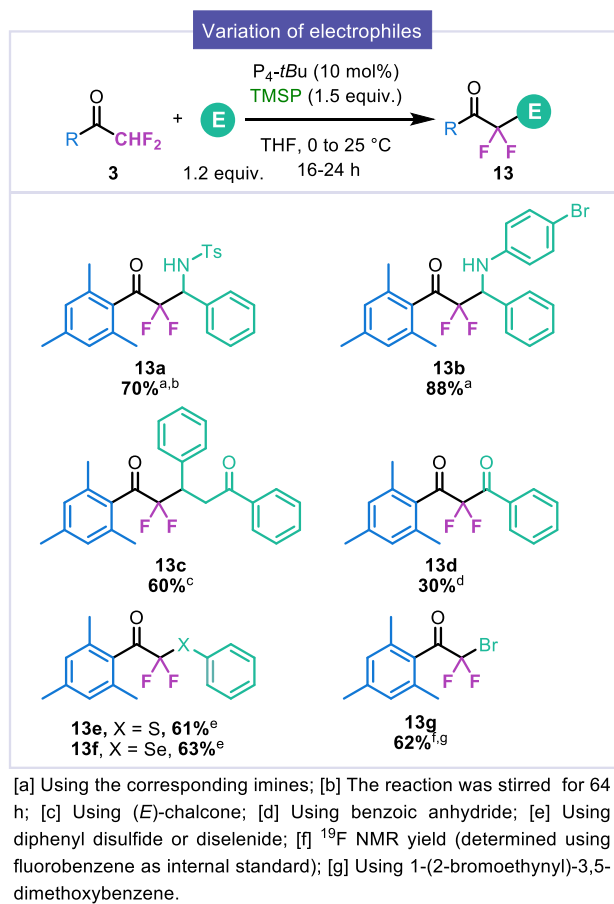


[a] ^{19}F NMR yield (determined using fluorobenzene as internal standard)

Scheme 5. Follow-up chemistry.

To go one step further, we envisioned to extend our method to other electrophilic partners (Scheme 6). Pleasingly, diverse electrophiles were well tolerated. The use of imines led to the formation of compounds **13a** and **13b** in high yields. By employing an α,β -unsaturated ketone, only the 1,4-addition compound **13c** was obtained in 60% yield contrary to the use of acrolein that only afforded the 1,2-addition product **4aa**. Next, diketone **13d** was obtained in 30% yield in the presence of benzoic anhydride. We also studied the reaction with chalcogen derivatives such as diphenyl disulfide or diphenyl diselenide giving the corresponding products **13e-f** with yields around 60%. Finally, using an alkynyl bromide, we managed to form α -bromo- α,α -difluoro- β -hydroxy ketone **13g** in 62% of NMR yield. Unfortunately, the compound could not be properly isolated since degradation always occurred during purification. To gain insight on this process using other electrophiles, control experiments were carried out in the absence of TMSF notably in the case of alkynyl bromide and dichalcogenides. As well as for the aldol reaction, a decrease in

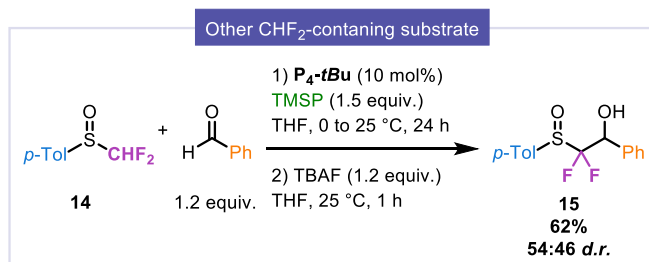
yield and conversion was noticed (see Supporting Information for more details). These results are consistent with the previous hypothesis that propyne generation is the driving force of the reaction.



[a] Using the corresponding imines; [b] The reaction was stirred for 64 h; [c] Using (*E*)-chalcone; [d] Using benzoic anhydride; [e] Using diphenyl disulfide or diselenide; [f] ^{19}F NMR yield (determined using fluorobenzene as internal standard); [g] Using 1-(2-bromoethynyl)-3,5-dimethoxybenzene.

Scheme 6. Deprotonation of α,α -difluoromethyl ketones in the presence of other electrophiles.

Furthermore, in view of our previous work on α,α -difluoromethyl sulfoxides,^[16a,c-d] we desired to assess them in our deprotonative functionalization strategy as an interesting electron-poor CHF_2 -containing alternative to difluoromethyl ketones (Scheme 7). Thus, by submitting racemic sulfoxide **14** in the presence of benzaldehyde to the above-mentioned conditions, the corresponding β -hydroxysulfoxide **15** was isolated in 62% yield and 54:46 *d.r.* Noteworthy, this selectivity has to be compared to the similar one obtained with stoichiometric potassium *tert*-butoxide as the base (ca. 60:40) whereas stoichiometric amounts of $\text{P}_4\text{-}t\text{Bu}$ led to 99:1 *d.r.* under kinetic resolution by degradation of one diastereomer.^[16c-d]



Scheme 7. Deprotonative functionalization of an α,α -difluoromethyl sulfoxide.

Conclusion

In conclusion, we have developed the first direct aldol reaction of α,α -difluoromethyl ketones *via* their deprotonation using a catalytic organosuperbase. This condensation proved to be highly efficient and led to a wide range of α,α -difluoro- β -hydroxy ketones in the presence of aryl, heteroaryl as well as alkyl aldehydes with yields up to 95%. We also managed to perform the diastereoselective version of the latter reaction using enantiopure aldehydes displaying central or axial chirality with diastereoisomeric ratios up to 93:7. Furthermore, we demonstrated the synthetic potential of the obtained α,α -difluoro- β -hydroxy ketones by submitting them to different transformations. Finally, this deprotonative functionalization strategy was applied to various other electrophiles such as imines or chalcogen derivatives giving access to highly valuable difluoromethylene compounds. The use of another CHF_2 -containing substrate, namely an α,α -difluoromethyl sulfoxide, was also well tolerated in this deprotonation process.

Experimental Section

The data that support the findings of this study are available in the Supporting Information of this article.

Acknowledgements

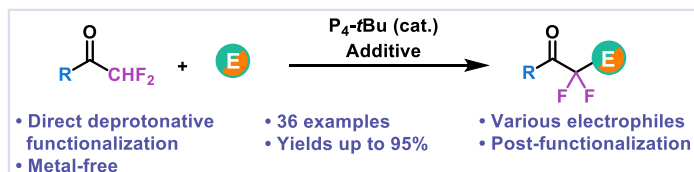
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Keywords: Aldol reaction • Deprotonation • Difluoromethyl • Difluoromethylene • Fluorine

- [1] a) A. Rodil, A. M. Z. Slawin, N. Al-Maharik, R. Tomita, D. O'Hagan, *Beilstein J. Org. Chem.* **2019**, *15*, 1441–1447; b) *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, (Eds.: G. Haufe, F. R. Leroux), Elsevier Science, London, **2018**, pp. 1–686; c) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880; d) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518; e) *Modern Synthesis Processes and Reactivity of Fluorinated Compounds*, (Eds.: H. Groult, F. R. Leroux, A. Tressaud), Elsevier Science, London, **2016**, pp. 1–760; f) C. D. Murphy, G. Standford, *Expert Opin Drug Metab. Toxicol* **2015**, *11*, 589–599; g) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359; h) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; i) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081; j) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305–321; k) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; l) *Bioorganic and Medicinal Chemistry of Fluorine*, (Eds.: J.-P. Bégue, D. Bonnet-Delpon), John Wiley & Sons, Inc., **2008**, pp. 1–365; m) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; n) P. Shah, A. D. Westwell, *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540; o) J.-P. Bégue, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992–1012; p) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; q) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; r) P. Maienfisch, R. G. Hall, *Chim. Int. J. Chem.* **2004**, *58*, 93–99; s) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11.
- [2] a) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; b) S. Pazenok, D. Bernier, M. Donnard, G. Hanquet, A. Panossian, F. R. Leroux, in *PATAI'S Chemistry of Functional Groups*, John Wiley & Sons, Ltd, **2022**, pp. 1–77.
- [3] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640
- [4] For recent reviews on the properties and synthesis of CF_2 -containing products see: a) S. Saphier, S. Katalan, G. Yacov, A. Berliner, O. Redy-Keisar, G. Fridkin, L. Ghindes-Azaria, I. Columbus, A. Pevzner, E. Drug, H. Prihed, E. Gershonov, Y. Eichen, S. Elias, G. Parvari, Y. Zafrani, *Chem. Eur. J.*, accepted, DOI: 10.1002/chem202202939; b) O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem*, accepted, DOI: 10.1002/cmdc.202200365; c) F. Zhao, W. Zhou, Z. Zuo, *Adv. Synth. Catal.* **2022**, *364*, 234–267; d) O. O. Grygorenko, D. M. Volochnyuk, B. V. Vashchenko, *Eur. J. Org. Chem.* **2021**, 6478–6510; e) D. R. Carvalho, A. H. Christian, *Org. Biomol. Chem.* **2021**, *19*, 947–964; f) D.-Q. Dong, H. Yang, J.-L. Shi, W.-J. Si, Z.-L. Wang, X.-M. Xu, *Org. Chem. Front.* **2020**, *7*, 2538–2575; g) Q. Xie, J. Hu, in *Emerging Fluorinated Motifs*, John Wiley & Sons, Ltd, **2020**, pp. 89–117; h) Y.-L. Xiao, X. Zhang, in *Emerging Fluorinated Motifs*, John Wiley & Sons, Ltd, **2020**, pp. 1–46; i) D. M. Volochnyuk, O. O. Grygorenko, in *Emerging Fluorinated Motifs*, John Wiley & Sons, Ltd, **2020**, pp. 135–194; j) S. Barata-Vallejo, A. Postigo, in *Emerging Fluorinated Motifs*, John Wiley & Sons, Ltd, **2020**, pp. 47–87; k) E. Carbonnel, T. Poisson, P. Jubault, X. Pannecoucke, T. Besset, *Front. Chem.* **2019**, *7*, 111.
- [5] a) S. Sadhukhan, J. Santhi, B. Baire, *Chem. Eur. J.* **2020**, *26*, 7145–7175; b) G. Pattison, *Eur. J. Org. Chem.* **2018**, 3520–3540.
- [6] a) G. B. Dreyer, B. W. Metcalf, *Tetrahedron Lett.* **1988**, *29*, 6885–6888; b) C. Han, A. E. Salyer, E. H. Kim, X. Jiang, R. E. Jarrard, M. S. Powers, A. M. Kirchhoff, T. K. Salvador, J. A. Chester, G. H. Hockerman, D. A. Colby, *J. Med. Chem.* **2013**, *56*, 2456–2465.
- [7] a) X. Gong, Q. Zhou, G. Yan, *Org. Biomol. Chem.* **2022**, *20*, 5365–5376; b) X.-S. Hu, J.-S. Yu, J. Zhou, *Chem. Commun.* **2019**, 55, 13638–13648; c) M. Decostanzi, J.-M. Campagne, E. Leclerc, *Org. Biomol. Chem.* **2015**, *13*, 7351–7380; d) H. Mei, C. Xie, J. L. Aceña, V. A. Soloshonok, G.-V. Rösenthaller, J. Han, *Eur. J. Org. Chem.* **2015**, 2015, 6401–6412.
- [8] For selected examples of Mukaiyama aldol reactions see: a) F.-M. Liao, X.-T. Gao, X.-S. Hu, S.-L. Xie, J. Zhou, *Sci. Bull.* **2017**, *62*, 1504–1509; b) J.-S. Yu, Y.-L. Liu, J. Tang, X. Wang, J. Zhou, *Angew. Chem. Int. Ed.* **2014**, *53*, 9512–9516.
- [9] For selected examples of Reformatsky reactions reactions see: a) H. Yao, C.-R. Cao, M. Jiang, J.-T. Liu, *J. Fluorine Chem.* **2013**, *156*, 45–50; b) T. Poisson, M.-C. Belhomme, X. Pannecoucke, *J. Org. Chem.* **2012**, *77*, 9277–9285; c) M. Kuroboshi, T. Ishihara, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 428–437.
- [10] For selected examples of aldol reactions promoted by trifluoroacetate release see: a) P. Zhang, C. Wolf, *Angew. Chem. Int. Ed.* **2013**, *52*, 7869–7873; b) P. Zhang, C. Wolf, *J. Org. Chem.* **2012**, *77*, 8840–8844; c) C. Han, E. H. Kim, D. A. Colby, *J. Am. Chem. Soc.* **2011**, *133*, 5802–5805.
- [11] For selected examples of aldol reactions by a Brook rearrangement see: a) M. Decostanzi, J. Godemert, S. Oudeyer, V. Levacher, J.-M. Campagne, E. Leclerc, *Adv. Synth. Catal.* **2016**, *358*, 526–531; b) O. Lefebvre, T. Brigaud, C. Portella, *J. Org. Chem.* **2001**, *66*, 1941–1946.

- [12] R. Doi, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2016**, *55*, 341–344.
- [13] S. Sasaki, T. Suzuki, T. Uchiya, S. Toyota, A. Hirano, M. Tanemura, H. Teramoto, T. Yamauchi, K. Higashiyama, *J. Fluorine Chem.* **2016**, *192*, 78–85.
- [14] P. Peng, J. Wu, J. Liang, T. Zhang, J. Huang, F. Wu, *RSC Adv.* **2017**, *7*, 56034–56037.
- [15] For selected examples of decarboxylative aldol reactions see: a) A. Tarui, M. Oduti, S. Shinya, K. Sato, M. Omote, *RSC Adv.* **2018**, *8*, 20568–20575; b) D.-K. Huang, Z.-L. Lei, Y.-J. Zhu, Z.-J. Liu, X.-J. Hu, H.-F. Mao, *Tetrahedron Lett.* **2017**, *58*, 3394–3397.
- [16] For our previous work on the deprotonation of difluoromethyl scaffolds see: a) A. Messara, N. Vanthuyne, P. Diter, M. Elhabiri, A. Panossian, G. Hanquet, E. Magnier, F. R. Leroux, *Eur. J. Org. Chem.* **2021**, 5019–5026; b) L. Santos, A. Panossian, M. Donnard, J.-P. Vors, S. Pazenok, D. Bernier, F. R. Leroux, *Org. Lett.* **2020**, *22*, 8741–8745; c) C. Batisse, M. F. Céspedes Dávila, M. Castello, A. Messara, B. Vivet, G. Marciniak, A. Panossian, G. Hanquet, F. R. Leroux, *Tetrahedron* **2019**, *75*, 3063–3079; d) C. Batisse, A. Panossian, G. Hanquet, F. R. Leroux, *Chem. Commun.* **2018**, *54*, 10423–10426.
- [17] a) N. Punna, T. Saito, M. Kosobokov, E. Tokunaga, Y. Sumii, N. Shibata, *Chem. Commun.* **2018**, *54*, 4294–4297; b) S. Okusu, K. Hirano, E. Tokunaga, N. Shibata, *ChemistryOpen* **2015**, *4*, 581–585; c) H. Kawai, Z. Yuan, E. Tokunaga, N. Shibata, *Org. Biomol. Chem.* **2013**, *11*, 1446–1450; d) Y. Zhang, M. Fujii, H. Serizawa, K. Mikami, *J. Fluorine Chem.* **2013**, *156*, 367–371.
- [18] For selected examples on the catalytic use of P_a-tBu by Kondo's group for non-fluorinated nucleophiles, see: a) Y. Araki, K. Kobayashi, M. Yonemoto, Y. Kondo, *Org. Biomol. Chem.* **2011**, *9*, 78–80; b) Y. Hirano, K. Kobayashi, M. Yonemoto, Y. Kondo, *Chem. Commun.* **2010**, *46*, 7623–7624; c) H. Naka, D. Koseki, Y. Kondo, *Adv. Synth. Catal.* **2008**, *350*, 1901–1906; d) K. Suzawa, M. Ueno, A. E. H. Wheatley, Y. Kondo, *Chem. Commun.* **2006**, 4850–4852; e) Kobayashi, M. Ueno, Y. Kondo, *Chem. Commun.* **2006**, 3128–3130; f) M. Ueno, C. Hori, K. Suzawa, M. Ebisawa, Y. Kondo, *Eur. J. Org. Chem.* **2005**, 1965–1968.
- [19] G. K. S. Prakash, J. Hu, G. A. Olah, *J. Fluorine Chem.* **2001**, *112*, 357–362.
- [20] E. Schmitt, B. Rugeri, A. Panossian, J.-P. Vors, S. Pazenok, F. R. Leroux, *Org. Lett.* **2015**, *17*, 4510–4513.
- [21] A. L. Trifonov, V. V. Levin, M. I. Struchkova, A. D. Dilman, *Org. Lett.* **2017**, *19*, 5304–5307.
- [22] E. Matador, M. de G. Retamosa, A. Jiménez-Sánchez, D. Monge, R. Fernández, J. M. Lassaletta, *Eur. J. Org. Chem.* **2019**, 130–138.
- [23] L. Feng, T. Hu, S. Zhang, H.-Y. Xiong, G. Zhang, *Org. Lett.* **2019**, *21*, 9487–9492.
- [24] a) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327; b) B. R. Langlois, T. Billard, *Synthesis* **2003**, 185–194; c) B. Folléas, I. Marek, J.-F. Normant, L. Saint-Jalmes, *Tetrahedron* **2000**, *56*, 275–283; d) B. Folléas, I. Marek, J.-F. Normant, L. Saint-Jalmes, *Tetrahedron Lett.* **1998**, *39*, 2973–2976.
- [25] Deposition number CCDC 2192082 for **4g** contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe [Access Structures](#) service.
- [26] N. Jacob, Y. Zaid, J. C. A. Oliveira, L. Ackermann, J. Wencel-Delord, *J. Am. Chem. Soc.* **2022**, *144*, 798–806.
- [27] G. Liao, H.-M. Chen, Y.-N. Xia, B. Li, Q.-J. Yao, B.-F. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 11464–11468.
- [28] R. Schwesinger, C. Hasenfratz, H. Schlemper, L. Walz, E.-M. Peters, K. Peters, H. G. von Schnering, *Angew. Chem. Int. Ed.* **1993**, *32*, 1361–1363.

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The deprotonation of α,α -difluoromethyl ketones is underinvestigated due to the instability of the generated carbanion that can evolve into a fluorocarbene. A method for the deprotonative functionalization of these compounds is described herein under an organocatalytic system using various electrophiles, and is also applied to a related α,α -difluoromethyl sulfoxide. This strategy gives access to highly valuable difluoromethylene scaffolds.

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